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EFFECTS OF NATURAL SELECTION ON HUMAN GENOTYPES

BY

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+Ruggero Ceppellini, of the Institute of Genetics, Milan, Italy, also presented a paper, "Selection and Hereditary Anemias," at the meeting upon which this publication is based. The material presented by him, an abstract of which appeared in *the Transactions of The New York Academy of Sciences* for November 1955, is to be published in *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 20, 1956, as a contribution to the discussion of the paper "Aspects of Polymorphism in Man" by A. C. Allison.

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SELECTION GENETICS IN MAN

By

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Introduction

Every individual has developed from a fertilized egg. This fertilized egg carries the entire hereditary potentiality of the future individual. The hereditary complement consists primarily of genes located on the chromosomes, one complete set of chromosomes being contributed by each parent. Each set contains many genes, each located at a definite locus on the chromosome. Each gene may exist in a number of alternative forms or alleles. The complete specification of the alleles present at each ocus of both sets is the genotype of the individual. The result of this genotype interacting with the environment during the development of the ndividual gives all the physical characteristics–morphological, physiological, and psychological–that we call the phenotype of the individual. n practice, neither the complete genotype nor the complete phenotype of any individual is ever known. Normally, geneticists consider only one aspect, or a relatively few aspects of the phenotype at a time, referring o the aspects in question as traits and to the specification of just these raits as *the* phenotype, for convenience. Similarly they will speak of *the* genotype as simply the specification of one or more loci where alternative alleles influence the trait in question. For example, one will talk of the ecessive gene for albinism, *a*, and its normal allele, *A*, and of the three genotypes *aa*, *aA*, and *AA*, the first of which produces the albino phenoype while the other two are normal. Actually, the gene *A* may have other unctions essential to life, but we recognize its existence only by the changes produced by its allele, *a*. In fact, complete loss of any gene usually prevents development, and even the changes produced by an allele are often quite varied, the most striking being recognized and giving the name to the locus.

On the other hand, there is not always (nor perhaps even usually) a direct 1:1 relationship between genotype and phenotype. The genotype produces simply a certain developmental potential or "norm of reaction" hat in turn produces given results in given circumstances. Thus the henotype produced depends on the environment provided. As an example, we may take the recessive trait, xeroderma pigmentosum. Persons with

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this condition are abnormally sensitive to sunlight, developing severe freckling and often skin cancer, but they can enjoy fairly normal lives if they avoid strong sunlight. Again, diabetes mellitus is a hereditary trait whose precise mode of inheritance is not known with certainty. Those cases of the disease developing early in life were formerly usually fatal. Now the provision of an environment that includes insulin injections enables these people to live nearly normal lives. In fact, if we imagine an environment where all adults were given insulin injections, the diabetics would be normal, while what we call the normals would be subject to the "disease" of insulin shock. Pursuing the subject further, some persons with a genotype predisposing to diabetes may remain normal in most environments, but may develop the disease in an environment where they overeat. It should be made clear that for a given completely specified genotype, the phenotype depends only on environment; but if by genotype we mean only the situation at those few loci that have been shown to affect a given trait, then the expression of that trait may also be affected by the residual unspecified genotype.

Finally, it should be noted that the "environment" refers not only to gross, obvious differences in environment, but also to subtle and unspecifiable differences. The result of the many undetectable differences in environment and residual genotype is that frequently we can talk only about the probability of expression of a trait in a given partial genotype. Such probabilities appear in our discussion of natural selection and in our discussion of the accompanying paper of McConnell.

Genes in Populations

An important aspect of genetics is the study of genes in populations. Let us concentrate our attention on a single locus at which, for the sake of simplicity, we consider only two alleles, A and A'. In a given population the three possible genotypes may appear in the relative proportions $bAA : cAA' : dA'A'$, where $b + c + d = 1$. Then the proportion of A genes in this population is $(2b + c) : (2b + 2c + 2d)$. Call this proportion q, and let $p = 1 - q$ be the proportion of A' genes. We say there is random mating if an individual has equal chances of mating with every individual of the opposite sex. Under these conditions the chance of any given sperm being A is q, and the chance of the ovum with which it unites being A is also q. Consequently, the three genotypes in the next generation would have the relative frequencies $q^2\ AA : 2pq\ AA' : p^2\ A'A'$, as shown in TABLE 1. These frequencies are known as the Hardy-Weinberg equilibrium frequencies. While the above conditions for random mating are never fulfilled, the conclusion is still valid if there is no tendency for males of a given genotype to mate preferentially with females of any particular

TABLE 1

GENOTYPES RESULTING FROM RANDOM COMBINATION OF GAMETES

eggs sperm	A	A'	Total
A	q^2	$q(1-q)$	q
A'	$q(1-q)$	$(1-q)^2$	$(1-q)$
Total	q	$1-q$	

enotype and no tendency for an excess of matings between relatives. hile there is probably some preferential mating for the genotype as a hole, these latter conditions hold to a good degree of approximation for uch things as the blood-group genes, and the Hardy-Weinberg frequencies old in practice for these and many other loci.

Even for the blood-group genes, however, there must be a proviso. e must be dealing with a homogeneous population. For many purposes, e white population of a city such as London may be sufficiently homo-eneous to allow the Hardy-Weinberg law to hold. On the other hand, it ould not hold if we took the average q for blood type A or thalassemia Sardinia. Here it would hold only within a village, since intermarriage etween villages is infrequent enough to have allowed considerable dif-erences in gene frequency to develop between them (see Ceppellini [1,2]).

Natural Selection

In the long run, not all genotypes are equally successful. Some are avored and some are opposed by natural selection, with resulting changes gene frequencies. From the point of view of natural selection and in espect to gene frequencies, the only thing that matters about a geno-pe is the number of offspring its possessor may be expected to produce. is essential that this figure be calculated over a complete life cycle; us we may consider a newborn child and its expected number of live-rn children, or an individual who has just reached reproductive age d the expected number of his children who also reach reproductive age, c. Fortunately for us, it is not necessary to know the absolute number offspring expected for a given genotype, but only its ratio to the value r some other genotype taken as the standard. This ratio may often be timated when neither individual value is known. We shall refer to these tios as selective values. Let us take as an example the case where a recessive dies before reproductive age, or is sterile, or is prevented from finding a mate, or is legally prevented from reproducing by sterilization or other means. Mathematically these are all the same. We may take the selective value of *aA* and *AA* as one, and the selective value of *aa* must be zero. This situation is represented in TABLE 2. As a result, the frequency of the *a* gene in the offspring will be

$$\frac{1}{2} \cdot \frac{2pq}{1-q^2} = \frac{q(1-q)}{(1+q)(1-q)} = \frac{q}{1+q}$$

Repeating the above process, if q_1 is the gene frequency in the first generation and q_n in the *n*th generation, we find $q_n = q_1/[1+(n-1)q_1]$. Letting r_n be the frequency of the recessive individuals at birth in the *n*th generation, TABLE 3 gives the values of q_n and r_n for certain values of *n* if initially $q_1 = 1/2$. It will be seen that even this total selection is not very rapid in reducing the frequency of rare recessive traits and that, consequently, sterilization is not very effective in eliminating rare recessive diseases.

If, on the other hand, the carriers or *Aa* individuals could be identified and sterilized also, we would have all the *a* genes eliminated in one generation. The desirability of taking so drastic a step is doubtful at best and becomes even more so in the light of two further considerations: (1) Many deleterious recessive genes may be advantageous in the heterozygous state. (For example, individuals heterozygous for the gene for sickle cell anemia or for Cooley's anemia are apparently more resistant to falciparum malaria. See, for example, Ceppellini.[1,2]) (2) Muller[6] has estimated that each of us is, on the average, the carrier of about eight deleterious genes in heterozygous condition, so it might not be advisable to sterilize the human race to eliminate a few rare diseases.

TABLE 2

COURSE OF SELECTION AGAINST A RECESSIVE LETHAL GENE *a*

Genotype	*aa*	*aA*	*AA*	*Total*
Frequency at birth	q^2	$2pq$	p^2	1
Selective value	0	1	1	
Frequency in reproducing population	0	$2pq$	p^2	$1-q^2$
Adjusted frequency	0	$\frac{2pq}{1-q^2}$	$\frac{p^2}{1-q^2}$	1

TABLE 3

VALUES OF GENE FREQUENCY q_n AND FREQUENCY OF RECESSIVE HOMOZYGOTE r_n AFTER n GENERATIONS OF SELECTION AGAINST A RECESSIVE LETHAL

n	1	2	3	4	5	6	9	13	19	31	44	99
q_n	$\frac{1}{2}$	$\frac{1}{3}$	$\frac{1}{4}$	$\frac{1}{5}$	$\frac{1}{6}$	$\frac{1}{7}$	$\frac{1}{10}$	$\frac{1}{14}$	$\frac{1}{20}$	$\frac{1}{32}$	$\frac{1}{45}$	$\frac{1}{100}$
r_n%	25	11.1	6.25	4	2.78	2.04	1	0.51	0.25	0.10	0.05	0.01

Genetic Equilibrium

Turning our attention from sterilization to purely natural forces, we ee that where the recessive dies before reaching reproductive age, even- ually the recessive gene will be completely eliminated, barring other rces. Let us examine some of these forces. The first to be considered s a selective advantage for the heterozygote.

The most general case of selection for a locus with two alleles that re not sex linked, and where the selective values are the same in both exes, can be represented by assigning selective values as indicated in ABLE 4. Since selective values are ratios, that is, are relative to some tandard, we take that of $A'A'$ to be 1. The frequency of gene A in the eneration after selection will be

$$q_2 = \frac{W_1 q^2 + W_2 pq}{W_1 q^2 + 2W_2 pq + p^2}$$

can be easily shown that if W_2 is greater than both W_1 and 1, there ill be a stable gene frequency, $\bar{q}$, which is called the equilibrium fre- uency. If q is less than $\bar{q}$ it will increase, if greater than q it will de- ease, and if equal to $\bar{q}$ it will remain unchanged. The value of q is $= (W_2 - 1)/(2W_2 - W_1 - 1)$.

TABLE 4

SELECTION FOR TWO ALLELES IN THE GENERAL CASE

Genotype	AA		AA'		$A'A'$
Frequency before selection	q^2		$2pq$		p^2
Selective values	W_1		W_2		1
Relative frequency after selection	$W_1 q^2$	:	$2W_2 pq$	:	p^2

Let us take the example considered by Ceppellini.[1,2] He supposes for thalassemia that all *mm* individuals have the disease and have selective value zero, and that the equilibrium frequency of heterozygotes among adults is 0.20. Since each of these carries one *a* gene, $\bar{q} = 0.10$ in adults. TABLE 5 shows what will happen. Since we are supposing we are already at equilibrium, we must have the final frequency of the *m* gene the same as the initial frequency; that is, $\frac{1}{2}\left(\frac{0.18\,W_2}{0.81 + 0.18W_2}\right) = 0.10$. Solving, $W_2 = 0.162/(0.180–0.036) = 9/8 = 1.125$. Substituting $q = 0.2$, $W_1 = 0$, $W_2 = 1.125$ in TABLE 4, we can verify that q will remain constant. We thus see that the frequency of 20 per cent for heterozygotes can be explained by assuming that homozygotes do not reproduce, but heterozygotes have a selective advantage of 12.5 per cent over "normal" homozygotes, due to superior survival, fertility, or other causes.

Of course there are other ways in which genetic equilibrium may be brought about. For example, we may have mutation. Referring to TABLE 5 and assuming the heterozygote has no advantage, that is $W_2 = 1$, we see that for every 100 genes, one *a* gene will be lost. If one of the 90 *A* genes mutates to *a*, the loss will be exactly compensated. Mutation is a well-known phenomenon, but from our knowledge of lower organisms and our limited knowledge of man, it seems that mutation rates are usually of the order of 1 in 50,000 to 1 in 1,000,000 or less, and the required mutation rate of 1 in 90 is extremely unlikely.

Another possible factor in causing equilibrium is compensation. Under some circumstances, parents of a child who dies of a hereditary or other disease compensate by having another child to take its place.

TABLE 5

PROPOSED COURSE OF SELECTION IN CASE OF THALASSEMIA

Genotype	*mm*	*mM*	*MM*	*Total*
Frequency after selection	0	.20	.80	1
Frequency at birth in next generation	.01	.18	.81	1
Selective values	0	W_2	1.	
Relative frequency after selection	0 :	$.18W_2$:	.81	$.81 + .18W_2$
Adjusted frequency	0	$\frac{.18W_2}{.81 + .18W_2}$	$\frac{.81}{.81 + .18W_2}$	1

is well known that there is often overcompensation, so that such milies ultimately have more than the normal number of children. Since, r a recessive disease, affected children can be born only to two hetero- gous parents, one third of the genes in the normal children from such marriage will be of the recessive type, and the excess children will nd to increase the gene frequency. In Africa the ultimate reproductive tential has probably been reached, so that no compensation is possi- e. There is some evidence for compensation in thalassemia, but it is obably insufficient to have a large effect on the gene frequency.

Relative Risks

R. B. McConnell[5] discusses a type of data which should become ore frequent as time goes on. One considers the frequency of some asily detectable genotype in persons with a certain disease, and com- ares this frequency with that in the general population from which these atients come. If the genotype is more common among persons with the isease than among the general population, the assumption seems justi- ed that persons with the genotype in question must have a greater robability of developing the disease. McConnell discusses the problem f defining the population, or populations, from which the diseased dividuals come, and of then obtaining a suitable control sample. We all suppose that all patients come from one population, which is known nd, ignoring questions of sampling error, estimate the relative risks of e disease in carriers and noncarriers of the genotype in question. A rther treatment, with standard error formula, is in Woolf (1955).[10]

For concreteness, let us consider diabetes in persons of blood roups A and AB versus O and B. Let A denote A and AB, $\bar{A}$ (not A) enote O and B; D denote diabetes, and $\bar{D}$ denote no diabetes. Let $P(A)$ enote the frequency of A in the general population, or the probability at a person selected at random is A or AB, and let $P(\bar{A})$, $P(D)$, $P(\bar{D})$ e the probabilities of $\bar{A}$, D, and $\bar{D}$. Finally, let $P(A \mid D)$ be the proba- ility that a person is A, given that he is diabetic (that is, the frequency f A in diabetics), $P(D \mid A)$ be the probability of diabetes in an A individ- al, *etc.*, and let $P(AD)$ be the probability that a person is both A and D.

The probability that a person is both A and D is equal to the proba- ility that he is A, times the probability that he is D if he is already A, r in symbols,

$$P(AD) = P(A) \cdot P(D \mid A) \qquad (1)$$

By the same reasoning,

$$P(AD) = P(D) \cdot P(A \mid D) \qquad (2)$$

Equating the right hand sides,

$$P(A) \cdot P(D \mid A) = P(D) \cdot P(A \mid D), \tag{3}$$

and dividing both sides by $P(A) \cdot P(D)$,

$$\frac{P(D \mid A)}{P(D)} = \frac{P(A \mid D)}{P(A)} \tag{4}$$

The right side of this last equation is the ratio of the A frequency in diabetics to the A frequency in the controls, and is known. The left side is the ratio of the probability of an A person developing diabetes to the probability of a person in the general population developing diabetes, and is hence known, even though neither of these probabilities of developing diabetes is itself known.

Similarly we have

$$\frac{P(D \mid \bar{A})}{P(D)} = \frac{P(\bar{A} \mid D)}{P(\bar{A})} \tag{5}$$

Again the right side is known, so we have the ratio of the chances of a not-A person developing diabetes to those of the population in general. Dividing EQUATION (4) by (5), $P(D)$ cancels out, and we have

$$\frac{P(D \mid A)}{P(D \mid \bar{A})} = \frac{P(A \mid D)}{P(A)} \Big/ \frac{P(\bar{A} \mid D)}{P(\bar{A})} \tag{6}$$

We thus have the ratio of the risk of diabetes in A to that in not-A, in terms of the known quantities on the right. Applying this to the data quoted by McConnell, we have $P(A \mid D)$ = A + AB in diabetics = 0.5268, $P(A)$ = A + AB in controls = 0.4501, $P(A \mid D) = 1 - 0.5268 = 0.4732$, $P(A) = 1 - 0.4501 = 0.5499$. Hence

$$\frac{P(D \mid A)}{P(D \mid A)} = \frac{0.5268}{0.4501} \Big/ \frac{0.4732}{0.5499} = 1.1704/0.8605 = 1.36, \tag{7}$$

or, on the face of these data, persons of types A or AB have a 36 per cent greater risk of developing diabetes than do persons of types O or B. Strictly speaking, the calculations should have been done separately for the different geographic localities with different A frequencies and the resulting ratios combined, but this would make only a minor change in the result. At first sight, it is surprising that the difference of only 0.0767 between A + AB frequencies in diabetics and controls corresponds to a difference of 36 per cent in the risks, but this emphasizes the importance of the findings.

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SELECTION AND THE ABO BLOOD GROUP LOCUS

By

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There have been many attempts to investigate possible selective advantages or disadvantages of the ABO blood groups, but most of the investigations have given negative or inconclusive results. A great stimulus to this work has been given, however, in recent years by the demonstration that persons with different ABO blood groups almost certainly have different susceptibilities to at least two diseases.

For a long time many workers have considered that the polymorphism of the blood groups must be maintained by a balance of selective agencies, different environments favoring different balances between the genes. The frequencies of the ABO groups vary widely over quite small areas, suggesting to Mourant (1954) that the genes at the ABO locus may be much more intensively subject to natural selection than are the genes at other blood group loci.

Fertility and Longevity

Though the evidence available may not yet be regarded as conclusive, it suggests that there is quite marked selection against heterozygous fetuses and infants when the mother is group O and the father is group A or group B.

Isoimmunization of a group O mother by a heterospecific fetus that is a secretor does occur, and many cases of hemolytic disease of the newborn due to anti-A or anti-B have been reported. The condition is usually milder than when due to anti-Rh, but it is sometimes fatal (Levine *et al.*, 1953).

That there may also be intra-uterine selection against the heterozygote is suggested by the data of Sjöstedt *et al.*, (1951), who investigated infertile marriages, and Matsunaga (1955), who studied the frequency of miscarriages in different matings.

Whether or not there is a deficiency of group A children from the mating of O♀ × A♂ is still undecided, and the collection of a single large series giving the blood groups of children and both parents is needed before the question of differential fertility of those of different ABO groups can be regarded as settled.

The strength of selection to which the Rh genes are subjected is dependent to some extent on the ABO gene frequencies. Levine (1943) noticed, and it has since been well established, that the parents of cases of hemolytic disease due to anti-Rh are more often compatibly mated on the ABO system than are unselected matings. Thus incompatibility of ABO mating seems to confer a definite protection against hemolytic disease due to Rh incompatibility, and the work of Grubb and Sjöstedt (1954) suggests that it may also be giving protection against intra-uterine deaths due to Rh.

Association with Disease

Not long after the discovery of the blood groups, data began to be published giving the blood groups of patients with various diseases. In most of the series the numbers involved were small. In patients suffering from mental diseases large numbers of groupings were reported, but the remarks of Neel (1955) with regard to genetic homogeneity of material are very pertinent when considering not only these data but also those data published in recent years.

The first demonstration of a statistically significant association of an ABO blood group with a disease was made by Struthers (1951). Struthers studied the blood groups of 400 children at autopsy and found that, compared with controls, there was an excess of group A in the 148 who had post-mortem evidence of bronchopneumonia. The difference was very highly significant ($P < 0.001$), and the results of a similar investigation in another area are eagerly awaited. If Struthers' findings are confirmed and the association can be regarded as proved, a strong negative selective value of the A gene will have been demonstrated, bronchopneumonia being one of the most important of the killing diseases of infancy.

Carcinoma of Stomach

A great stimulus to other investigations into possible relationships between blood groups and disease was the finding of a significant association between blood group A and carcinoma of the stomach by Aird *et al.* (1953). The blood groups collected from 3,632 cases of carcinoma of the stomach showed a highly significant increase of group A over the A frequency in control series of other patients from the same hospitals. The seven different areas in Great Britain where data were collected were homogeneous in showing this association, and an equally significant excess of group A in 704 cases in Switzerland was also reported. The same association has also been found in 413 cases in Denmark (Køster *et al.*, 1955).

One point that may be of importance emerged from the further analysis by Aird *et al.* (1954). Sex had been recorded only in 1,000 of the cases, but these showed a marked though statistically insignificant difference between the blood-group distribution of males and females with gastric carcinoma. The 633 men showed the excess of group A whereas the 367 women had almost normal blood-group frequencies. There is need for further investigation of this point, especially in view of the finding of a sex difference in the blood groups of patients with diabetes mellitus, which will be described later in this paper.

Peptic Ulcer

Aird *et al.* (1954), a year after publishing their findings on carcinoma of the stomach, reported data showing an association between blood group O and peptic ulcer that was even more marked than the association between group A and gastric carcinoma. In 3,011 cases from three centers in England the percentage increase of group O over the O frequency in blood-donor controls was 17.9 per cent, and the three areas were homogeneous in this respect. These investigators did not find a significant difference between the frequencies in duodenal and gastric ulcer, although their data did suggest that there might be a real difference between them.

Aird *et al.* considered that, if their series were typical, persons of group O are 35 per cent more likely to develop peptic ulceration than are persons of other groups. This association of blood group O with peptic ulcer has also been found in Norway (Westlund and Heistö, 1955) and in Denmark (Køster *et al.*, 1955).

Duodenal Ulcer and Gastric Ulcer

C. A. Clarke and his colleagues in Liverpool, while much impressed with the findings of Aird *et al.* (1954), considered that it was probably unjustifiable to add duodenal ulcer data to gastric ulcer data and to analyze the combined data as "peptic ulcer." With such marked differences as regards sex and social distribution, age at onset, precipitating factors, and gastric acidity levels, it seemed likely that the two types of ulcer have different genetic backgrounds. Doll and Kellock (1951) had shown that the two diseases are probably inherited independently. Clarke and his colleagues therefore decided to make an investigation similar to that of Aird *et al.* and to differentiate carefully between duodenal and gastric ulcers (Clarke *et al.*, 1955).

They studied the records of 1,237 macroscopically proved ulcer patients blood-grouped in three Liverpool hospitals, and rejected all cases in which the exact site of the ulcer was uncertain (mainly juxtapyloric) and all cases in which both duodenal and gastric ulcers were found. They were left with 860 duodenal ulcers and 377 gastric ulcers. As controls, they used the 15,377 other patients who had been grouped in the same hospitals. Their findings are in agreement with those of

Aird *et al.* (1954) in that there is a very large increase in the frequency of group O in the duodenal ulcer patients compared with the controls. In the gastric ulcer patients, however, there is a normal blood group distribution and, in this, the data differ from the previous series.

Aird *et al.* (1954) analyzed their data in such a way that new information, as it is obtained, can be combined with theirs. When this is done with the data of Clarke *et al.* (1955) there is still no significant heterogeneity between different areas for any of the comparisons made. The difference between duodenal ulcer and the controls becomes even more highly significant, and there is still a significant difference between gastric ulcer and the controls, although the χ^2 has been reduced. The addition of the new data makes the difference between the blood-group distributions of duodenal ulcer and gastric ulcer highly significant. The details of these comparisons in the combined data are shown in TABLE 1.

From the new investigation the following conclusions can be drawn:

(1) There is a highly significant increase in the frequency of blood group O among duodenal ulcer patients when compared with that in the general population from which the patients came.

(2) There is a significantly higher group O frequency in duodenal ulcer patients than in gastric ulcer patients.

(3) Though gastric ulcer patients may have a higher group O frequency than that of the general population, the difference cannot yet be regarded as definitely established, and there is a suggestion that gastric ulcer patients may have normal blood-group frequencies.

Diabetes Mellitus

After it became known that there is a significant relationship between blood group O and duodenal ulcer in England, it was decided to investigate the ABO groups of patients with diabetes mellitus. It has been suspected that the frequency of duodenal ulceration is considerably lower

Table 1

Tests of Significance for the Ratio $\frac{A}{(A+O)}$
Combining the Data of Clarke *et al.* (1955)
with those of Aird *et al.* (1954)

Comparison	*Weighted mean difference %*	*χ^2 for difference (D. of F. = 1)*	*P*	*χ^2 for heterogeneity of areas (D. of F. = 5)*	*P*
D. U.—controls	−9.69	92.74	<0.001	7.59	>0.1
G. U.—controls	−3.99	7.89	<0.01	6.45	>0.2
G. U.—D. U.	+5.61	10.68	<0.01	4.55	>0.3

in diabetics than in the general population (Joslin, 1947), and it was thought that a possible reason for this might be that diabetics have a low group O frequency.

A grouping was made of 833 patients attending the Diabetic Clinic of the David Lewis Northern Hospital, Liverpool, England.

Blood-donor data showed that the Liverpool region, from which the patients came, is not homogeneous with regard to blood-group frequencies, and it was necessary to consider those patients who lived in West Cheshire separately from those who lived elsewhere in the Liverpool region. There had been 500 diabetics blood-grouped in Oxford, and it was decided to make an analysis of the diabetics from the three areas, each area having a different control series. This analysis (McConnell *et al.*, 1956) has shown a very remarkable homogeneity in the three areas, whatever subdivisions of the data were analyzed.

The main finding is that, compared with controls, there is an increase in the frequency of group A in the male diabetics, whereas the females have a normal blood-group distribution. This is shown in TABLE 2.

TABLE 2

GROUP PERCENTAGES IN PATIENTS WITH DIABETES MELLITUS

Blood group	*484 Males*			*849 Females*		
	Weighted control	*Disease*	*% increase or decrease on control*	*Weighted control*	*Disease*	*% increase or decrease on control*
O	46.12	40.29	−12.6	46.26	45.23	−2.2
A	42.01	49.17	+17.0	41.98	42.17	+0.5
B	8.87	7.03	—	8.80	8.13	—
AB	3.00	3.51	—	2.97	4.48	—

The examination of the differences in the proportions of those who possess gene A, and of the homogeneity of the areas gives the following results:

	Per cent difference in $\frac{(A+AB)}{(O+A+B+AB)}$	χ^2 for difference (D. of F. =1)	χ^2 for heterogeneity of areas (D. of F. =2)
Diabetic males—controls	+7.17	11.04	0.69
Diabetic females—controls	+1.70	0.93	0.31
Diabetic males—diabetic females	+5.91	4.33	0.60

The relative increase of gene A in the men is thus fairly significant (P = 1 in 1,120). The finding of a sex difference could hardly have been anticipated and is peculiar, though there is a possibility that it also exists in relation to carcinoma of the stomach. A direct comparison of the men and women patients also yields a significant difference.

Various other subdivisions have been analyzed, but without revealing any further significant differences. The excess of group A in the males is found at all ages, there being a significant difference from the controls both in those with onset of diabetes before 30 years of age and in those with onset after 30 years of age. There is no significant difference in the blood-group distribution of either the males or females having insulin compared with those controlled without the use of insulin.

A similar investigation has been carried out in Glasgow, Scotland, (Craig and Wang, 1955) in which no excess of group A has been found in 276 male diabetics. If Glasgow is considered a fourth area and the data from that region is added to that of the other three areas, χ^2 for the combined weighted mean difference in the proportion of those with gene A is reduced from 11.04 to 6.77; χ^2 for heterogeneity of areas is increased from 0.69 to 4.96, a figure not significant at the 5 per cent level. Hence, the findings in Liverpool and Oxford are not positively contradicted by the Glasgow data, but the probability that the finding of an excess of group A was due to chance has been increased from 1 in 1,120 to 1 in 110.

Are the Associations Merely Ethnological?

What has been demonstrated thus far is that, in certain racially mixed populations, patients with some diseases have higher frequencies of certain blood groups than those found in the general populations in which the patients live. This is what would be expected if the populations had in them racial groups that happened to have a high susceptibility to the diseases and blood group frequencies different from those of the rest of the population. Can we say that the associations found are due to such racial stratification, or are they etiological, certain of the ABO alleles conferring selective advantages or disadvantages with respect to certain diseases?

One way this question could be answered would be by an investigation of the blood groups of the sibs of affected individuals. If the associations found are merely due to high-incidence strains in the populations, then there should be the same blood-group frequencies in the unaffected sibs as in those affected with the diseases. On the other hand, if the associations are due to a direct etiological relationship, the blood-group frequencies of the affected individuals should be different from those of their unaffected sibs. In the case of an indirect etiological relationship, such as a maternal effect, the blood-group frequencies of affected and unaffected sibs would be similar. This type of investigation would appear to be particularly suited to countries with racially mixed populations and where the blood donors may not represent a good cross section of the population.

A sibship investigation of the ABO groups and duodenal ulcer has been in progress in Liverpool for over a year. Sufficient numbers have not yet been collected to make a definite conclusion possible, but the results so far do not contradict the existence of a relationship between duodenal ulcer and blood group O within the sibships.

An investigation of this type has the difficulties often encountered in a pedigree study but on a much larger scale. While there is no shortage of duodenal ulcer propositi, it is not always easy to contact their sibs and persuade them to cooperate. Long periods of time are therefore needed in order to obtain sufficient numbers for analysis. It is to be hoped, however, that similar investigations, if they are not already in progress, will be carried out, especially in the United States.

TABLE 3 shows the numbers and percentages of propositi, affected and unaffected sibs, with the different blood groups, in the first 168 sibships collected. The figures in this table indicate a higher group O frequency in the propositi and the affected sibs than in the unaffected sibs. In view of the unequal numbers of sibs in different families, however, these figures cannot be analyzed as they stand. The whole point of this investigation is to get a control that cannot be criticized on the grounds that it is not from the same population as the ulcer patients. Analysis, therefore, has to be made within families which segregate for blood group. When this is done with the data available so far, a group O individual does not appear to be any more likely to have an ulcer than his sibs of the other ABO groups.

Although this sibship investigation has not yet progressed far enough to give an answer to the problem of whether or not the association between blood group O and duodenal ulcer is causal, it is described

TABLE 3

NUMBERS AND PERCENTAGES IN 168 DUODENAL ULCER SIBSHIPS

Blood group	*Propositi*		*Affected sibs*		*Unaffected sibs*	
	Number	%	*Number*	%	*Number*	%
O	99	58.9	30	63.8	161	54.9
A	47	27.9	14	29.8	91	31.0
B	16	9.5	3	6.3	30	10.2
AB	6	3.5	0	0	11	3.7

at this stage in order to give the background to some secretor/nonsecretor data described later in this paper.

Possible Mechanisms of a Causal Relationship

If the relationship of the ABO groups to duodenal ulcer and carcinoma of the stomach is of a causal nature, the mechanism may be due to the action of the blood group antigens or may be due to a pleotropic effect of the ABO genes. Sheppard (1953) suggested that whether or not a person was a secretor of his blood group antigens might be an important factor in the susceptibility to gastric carcinoma. An investigation of the secretor status of patients with carcinoma of the stomach has been carried out since that time and, later, those with duodenal ulcer were included in the work.

The ability to secrete blood-group antigens in body fluids is inherited as a dominant character. Blood group A secretors have group-specific substance A in their body fluids, and blood group B secretors have group-specific substance B. The body fluids of blood group O secretors contain H-substance, which is not group-specific but is also found in secretors of groups A and B. Eel serum has been used as a source of anti-H, and all the tests have been carried out on saliva. It will be seen in TABLE 4 that in the control series of students and soldiers there is a much higher percentage of group O persons scored as nonsecretors than are scored by controls of the other groups. This has been found by previous workers, and Race and Sanger (1954) consider it to be an expression of technical difficulties. Since the incidence

TABLE 4

NUMBERS OF CONTROLS AND PATIENTS SCORED AS SECRETOR OR NONSECRETOR

Blood group	*Secretor status*	*Controls* ♂	*Controls* ♀	*Duodenal ulcer* ♂	*Duodenal ulcer* ♀	*Gastric carcinoma*
O	S	92	22	120	15	23
	ss	51	20	86	25	17
A	S	98	28	64	5	35
	ss	32	9	33	6	14
B	S	29	10	21	1	6
	ss	10	2	11	1	0
AB	S	7	4	6	0	1
	ss	0	1	5	0	0

Symbols: S = secretor; ss = nonsecretor.

of Le(a+b−) in England is about 22 per cent, whatever the ABO group, the incidence of nonsecretors should be only slightly over this in persons of all four ABO groups.

The difference from the expected nonsecretor incidence in the group O of the control series may be due to the fact that diluted saliva had been tested. It has only recently been realized that an appreciable number of group O secretors [as shown by having Le(a−b+) red cells and by inhibition tests with other kinds of anti-H sera, for instance those of human or vegetable origin] are able to inhibit eel serum only if three volumes of undiluted saliva to one volume of calibrated antiserum are used (Ceppellini, personal communication). Ceppellini estimates that with the usual technique, 10 to 30 per cent of group O secretors, depending upon the particular batch of eel serum used, may fail to show any inhibition and, in this series, they will have been scored as nonsecretors. An extract of the seeds of *Ulex europeus* is a much more satisfactory source of anti-H than is eel serum and will be used in the future. In the data presented in this paper, however, all the patients were tested, using the technique with eel serum that gave 38 per cent nonsecretors in the controls of group O.

In this investigation of secretor status, therefore, the results in persons of group O should be considered separately from those of groups A, B, and AB in whom the technique used is apparently satisfactory, there being no heterogeneity between the frequency of nonsecretors of these groups either in the controls or in the disease series.

Secretion in Carcinoma of Stomach and Duodenal Ulcer

Saliva has been collected from a series of unrelated cases of carcinoma of the stomach and duodenal ulcer. The results of the secretor tests in the control series and in the patients are given in TABLES 4 and 5.

The number of carcinoma-of-the-stomach patients tested is too small to make any conclusion possible but, so far, their nonsecretor incidence is very similar to that in the control series. The proportion of nonsecretors in the duodenal ulcer patients of all four blood groups and in both sexes is higher than that in control series. TABLE 6 shows the results of comparisons made. In each comparison the difference is in the same direction, and the sum of the χ^2s shows that the probability of getting this result by chance is between 1 in 20 and 1 in 50.

Secretion in Duodenal Ulcer Sibships

Saliva specimens have been collected whenever possible in the previously described investigation of the blood groups of duodenal

TABLE 5

PERCENTAGES OF NONSECRETORS

Blood group	*Controls*	*Duodenal ulcer*	*Gastric carcinoma*
O	38.3	45.1	42.5
A, B and AB	23.4	36.6	21.4

ulcer patients and their sibs. In 129 of the sibships, data are available on the secretor status of the propositus and of at least one sib, and are given in TABLE 7.

As found in the comparison between duodenal ulcer patients and controls, there is a higher incidence of nonsecretors in the duodenal ulcer patients than in their unaffected sibs. The percentages of nonsecretors are shown in TABLE 8.

As previously explained, these figures cannot be analyzed as they stand, owing to unequal numbers of sibs in different families. Analysis has to be made within families and, when this is done with the sibship secretor data, a significant association between nonsecretor and duodenal ulcer is found. No definite conclusions should be drawn at this stage, however, because of the error in the scoring of the group O members of the sibships.

Discussion of Secretor Findings

It is considered that these data strongly suggest a relationship between duodenal ulcer and nonsecretion. Though by no means conclusive, the differences found are sufficient to make it worth-while to

TABLE 6

COMPARISONS OF
SIGNIFICANCE OF NUMBERS OF SECRETORS AND NONSECRETORS

Blood group	*Comparison*	χ^2 *for difference (D. of F. = 1)*
O	♂ D.U. – ♂ control ♀ D.U. – ♀ control	1.07 1.28
A, B and AB	♂ D.U. – ♂ control ♀ D.U. – ♀ control	4.19 3.72

Total χ^2 (D. of F. =4) 10.25

continue the investigation. It would be of great benefit if the secretor tests could be accompanied by tests for Le^a, and it is hoped that similar investigations will be carried out at other centers.

Owing to the probability that the technique used in testing the saliva of group O persons has been faulty, it would be unwise to compare the secretor frequencies in those of different blood groups. Aird (1955) has suggested that the high incidence of blood group O in duodenal ulcer patients might be due to all the antigens, which are mucopolysaccharides, giving protection against ulcerogenic agents affecting the gastroduodenal mucosa, the H substance of group O persons giving less protection than A or B substance. The results of this investigation would support Aird's theory in that there is an increase in the nonsecretor frequency in ulcer patients of all four blood groups, but the question of relative increase in those of different blood groups cannot be answered. If the sibship investigation of blood groups should result in the conclusion that the associations already found in various areas are due to racial stratification in the populations, it would be difficult to understand why there should be a relationship with nonsecretion. It seems very unlikely that the disease, duodenal ulcer, could modify the secretion of blood group antigens.

The results of the secretor tests in the small group of patients having carcinoma of the stomach are inconclusive. Aird (1955) postulated that the antigens secreted might give protection against carcinogenic agents, but the present data do not support that theory. Much larger numbers of patients with gastric cancer will have to be tested before any conclusions can be drawn.

Selection, Duodenal Ulcer, Gastric Carcinoma, and Diabetes Mellitus

It is difficult to estimate the strength of the selection against the O gene if it really predisposes to duodenal ulceration. On the data that we have, it is probable that persons of group O are about 37 per cent more likely to develop duodenal ulcer than are persons of the other groups. In the past few decades duodenal ulcer has been a common disease, often having its onset between 15 and 25 years of age. Though its incidence is difficult to assess accurately, probably about 5 per cent of males in England are affected, and its death rate in males is 80 to 90 per million population. It affects males about six times more frequently than females, not infrequently causes early death (5 per cent of deaths due to duodenal ulcer are before 35 years of age), and probably has slight effects on the reproduction of those affected. There is, however, a great deal of evidence that duodenal ulcer is a disease of civilization and, particularly, of modern civilization. In the African Negro

TABLE 7

SECRETORS AND NONSECRETORS IN 129 DUODENAL ULCER SIBSHIPS

Blood group	*Secretor status*	*Propositi*	*Affected sibs*	*Unaffected sibs*
O	S	39	11	78
	ss	39	9	36
A, B and AB	S	33	9	71
	ss	18	4	23

duodenal ulceration is very rare among those living under tribal conditions, while it is not uncommon among those who lead a European type of life in the cities. The weight of evidence is in favor of the view that duodenal ulcer was an uncommon condition in England up to the latter part of the last century. In generations prior to that time, therefore, selection against the O gene because of duodenal ulceration must have been very slight.

Carcinoma of the stomach also affects males much more frequently than females. Until 10 years ago it was the most common cancer in men in Great Britain, but it only rarely occurs before 40 years of age and its effect on reproduction must be even less than that of duodenal ulcer. It seems likely that group A persons are about 20 per cent more likely to develop carcinoma of the stomach than are persons of the other group.

Diabetes mellitus, however, often occurs in childhood and, in 20 to 25 per cent of diabetic males, the onset of the condition is before 30 years of age. Before the discovery of insulin, diabetes in the young was nearly always rapidly fatal, and an association with the disease would be quite strongly selective against the A gene.

TABLE 8

PERCENTAGES OF NONSECRETORS IN 129 DUODENAL ULCER SIBSHIPS

Blood group	*Propositi and affected sibs*	*Unaffected sibs*
O	48.9	31.6
A, B and AB	34.3	25.5

Summary

(1) It is probable that the polymorphism of the ABO blood groups in particular environments is maintained by a balance of selective forces.

(2) There is evidence of selection against ABO heterozygotes in intra-uterine and neonatal life.

(3) It is still uncertain whether the associations found between the ABO groups and duodenal ulcer, carcinoma of the stomach, diabetes mellitus, and bronchopneumonia of infancy are causal or merely due to racial stratification in the population investigated. The associations with gastric cancer and duodenal ulcer have been found in so many different areas, however, that it seems likely that they are due to etiological relationships.

(4) The data suggest that persons of blood group O are about 37 per cent more likely to get duodenal ulcer than are persons of the other ABO groups, while persons of blood group A are about 20 per cent more likely to develop carcinoma of the stomach than are those of the other groups.

(5) The physiological explanation of the relationships is more likely to be due to an action of the blood-group antigens than to a pleotropic effect of the ABO genes. In duodenal ulcer, at least, there may be a relationship with nonsecretion, which may be of more importance than the relationship with group O.

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SELECTION IN RELATION TO RACE FORMATION AND EVOLUTION

By

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The last 20 years have seen a great upsurge of interest in the mechanism of evolution, and this has led to improved understanding of the meaning of evolution and to renewed hopes of elucidation of the evolutionary forces acting on human populations. The reason for this is not difficult to identify. It is the effect of the disclosure of the transmission mechanism of heredity and of the successful application of the ideas and methods of genetics to the problem of how observed changes in the genetic constitutions of experimental populations of animals and plants have come about. Some of the agencies leading to alterations in the relative frequencies of the variety of genotypes that occur within each cross-breeding population have been identified and subjected to analytical study.

This phase of the modern study of evolution was ushered in by the appearance in 1930 and 1931 of two seminal publications: R. A. Fisher's book *The Genetical Theory of Natural Selection*,[6] and Sewall Wright's classic paper "Evolution in Mendelian Populations."[15] Its climax was foreshadowed in T. Dobzhansky's *Genetics and the Origin of Species* in 1937,[4] and was confirmed in the subsequent revisions of this book in 1941 and 1951. Its maturity is witnessed in two books that appeared in 1955: C. C. Li's *Population Genetics*,[11] E. B. Ford's *Moths*[7] (which contains a summary of recent work on animal populations) and, in 1954, in *Genetic Homeostasis*, by I. M. Lerner.[9] G. G. Simpson's *Meaning of Evolution*[14] shows how these ideas have been used by a paleontologist in a masterly synthesis, for the general reader, of the whole range of evolutionary biology.

Evolution can now be viewed both as a process by which species and higher categories differentiated and developed in the past (which was the classic meaning given to it by Charles Darwin), and as a continuous and continuing process acting today to produce and maintain the adaptation of populations to their environments, which is so marked a feature of successful species. This can be seen today in the great diversity of the human populations in different parts of the world. We know that the major groups, such as the races into which mankind can be classified by anatomical features, differ from each other genetically. This genetic diversity can be described when we can identify specific hereditary elements, such as the genes determining different antigens or other properties of the blood, and when the frequencies of the same genes can be shown to be statistically different in different populations. Evolutionary changes can be said to have occurred when such statistical differences are regularly found in adequate samples. The justification for regarding such changes as constituting steps, albeit perhaps small ones, in evolutionary change is the experience of the past 20 years that such steps are necessary in the origination of wider diversity.

Our problem with human populations then, is to identify and study the causal factors responsible for diversity. The elementary step by which changes in genes occur is mutation: the process by which an existing form of a gene gives rise to another form or allele of the same element. Since the chemistry and physics of this change are not known (although this change is nonetheless an observable fact) we may view mutation as an accident in gene reproduction by which an imperfect copy rather than, as is usual, a perfect one is made when the cell multiplies during growth or at the maturation of the reproductive cells. Once a variety of gene alleles has arisen, these varied alleles are brought into a great variety of combinations in bisexual reproduction. The agencies that change the frequencies of these genes within a population are the evolutionary forces for which we seek.

Natural selection, to judge by the observations on nonhuman populations, appears to be the most universal of these agencies. Even though migration and accidents of sampling in small populations may cause local changes in the frequencies, the assemblage of genes must still be such as to permit successful occupation of an environment. As yet, there has not been much progress in connecting specific human genotypes with specific selective agents. That is why the material presented in this symposium is of such importance for future work. We may therefore consider for a moment the way in which this material bears on problems of human evolution.

A question of perennial interest is how the races of man were formed. It is a fact that major racial complexes of continental dimensions, such as African, White European, Australian, Asiatic, and American Indian show marked differences in the frequencies of certain blood-group genes. Europe is distinguished from all other continents by a relatively low frequency of the Rh-positive reaction, which in the Basques (whom some anthropologists regard as the prototype of the Europeans) reaches its lowest world frequency of less than 70 per cent, while elsewhere it is almost universally present. In most of Africa south of the Sahara, one particular Rh-positive gene (cDe) is very common, even characteristic. Elsewhere it is rare. American Indians are distinguished from their putative ancestors in Asia by having no blood-group B allele while, in

Asia, B reaches its highest world frequency. On the other hand, most American Indians are of blood group O with a lower frequency of A, while in Europe and Africa all three forms of this gene are more evenly mixed in the population. On a smaller scale, we find in the island of Sardinia, as R. Ceppellini[1] has pointed out, a frequency of MN genes sharply different from that of any neighboring area. Long-separated Jewish communities in Tripolitania, Iraq, and South India (Cochin) have markedly higher B frequencies than the populations within which they live. (Gurevitch *et al.*, 1955).[8] The newest antigen to be described (V) seems to be present in 25 to 30 per cent of African Negroes but in only .02 per cent of the English population—a 150-fold difference (De Natale *et al.*).[3] How do such differences come about?

Following earlier unsuccessful attempts to find connections between blood antigens and disease, which might alter the prospects for passing such genes to descendant generations, the view gained currency that such genes were selectively neutral. This left as an alternative the chance factor of random drift of frequencies through accidents of sampling in small populations. Those who sought in the blood-group genes tools for tracing racial affinities and phylogenies saw in the assumed selective neutrality and stability of these elements (no case of recent mutation in a blood-group gene had been proved) advantages as ethnographic criteria.

The proof of connection between the Rh genotypes and erythroblastosis fetalis dealt the first blow to this view, and a mechanism was clearly shown by which fairly rapid changes in the relative frequencies of Rh-positive and -negative genes could occur when one of the alleles was infrequent. A similar but less drastic effect of selection on the alleles of the Kell-Cellano blood factor and, possibly, on other alleles is indicated.

As we have seen, there is direct and convincing evidence that in England and Scandinavia and, probably, in similar societies, persons of blood-group O run a markedly greater risk of developing duodenal ulcer than those of groups A, B, or AB, while group A people run a lesser but still appreciable risk from gastric carcinoma. It seemed at first as though these risks might be chiefly determined by single genes, but such views in genetics usually prove to be illusory, and such was the case here. The genetically determined secretor status, the environmental predisposing factors such as those found in Western industrial societies, and possibly others also are involved. Consequently, if the relative frequencies of the ABO genes are altered, it will be through the interaction of genetic factors during development and through the reaction of these with the environment. This is probably true of selective effects in general.

Other effects of selection on the ABO frequencies are to be inferred from the marked heterogeneity of these genes as we pass from one community to another within the same geographic or ethnic group. Thus the increase in the frequency of blood group O from south to north in Britain cannot be used, by itself, as a criterion of ethnic differences until it is shown that the same selective or other causes of alteration play upon all areas. Similarly, when nearby villages agree in the frequency of one pair of genes, as M and N in Sardinia, but disagree in another, as in the case of the ABO genes, we have to conclude that the latter cannot be used, by themselves, as a part of the racial diagnosis of the Sardinian population. A. E. Mourant,[12] after a survey of the world distribution frequencies of the ABO genes that are subject to extreme geographic fluctuations, has already expressed his doubts as to their usefulness by themselves in ethnography.

Some of the limitations of the gene-frequency method in anthropology are well illustrated by the cases of the sickling and thalassemia genes. High frequency of the sickling genes has been regarded as characteristic of Africa, and that of the thalassemia genes as characteristic of certain Mediterranean peoples. Now there is reason to believe that both may be subject to alteration by environmental factors peculiar to certain areas, such as the distribution of a malarial parasite and its insect vectors. This does not alter the fact that sickling and thalassemia are inherited. It does suggest that the importance of other components of the nature-nurture complex that jointly determine the outcome of the gene-transmission must be estimated before the ethnographic usefulness of the genes can be evaluated. In the case of these two hereditary anemias, another problem arises. In certain areas—in eastern Sicily, for example—both genes have rather high frequencies, and the likelihood has to be reckoned with that some people will be heterozygous for both. If, as E. Silvestroni[23] has suggested, these double heterozygotes (or some of them) suffer from anemias with morbidity rates comparable to those of either of the homozygotes, then the frequency of one gene will be a factor in reducing the frequency of the other. This is another aspect of the genetical environment of the gene to be taken into account in evaluating its ethnographic usefulness. If the two genes react to different degrees with the malarial component, then a more complex situation arises, but one that, as Howard Levene[10] has shown, can be dealt with mathematically when the several parameters can be estimated.

It is evident that future research on the effects of selection on human genotypes must be planned with these situations in mind. Very little is known, for example, about the interactions between the different blood-group systems. It is probable, on the basis of the observations of R. Grubb[5] and R. Ceppellini, for example that the ABO and Lewis groups and the secretor status are parts of an interacting complex. There are indications from observations of P. Levine, R. Grubb, and others that Rh and ABO genes interact. The future of such work is now fraught with hope. The evidence of greater complexity is itself an augury of progress, since it means that some of the elements in the complex can be recognized. It is of great importance that the attention of those engaged in medical practice and research is now alerted to these possibilities, and the clinical significance of human genotypes will be increasingly recognized. Perhaps it is not too much to expect that those interested in actuarial work and vital statistics may turn some part of their attention to the relation between genotype (in respect to the blood-group systems, for example) and life expectancy.

While work of this sort is proceeding, we may perhaps suspend judgment on the ethnographic position of the genes involved. Surely evaluation of the effects of selection on human genotypes should be an important, even a prime desideratum in the development of racial anthropology. A recognition of this view and a discussion of its prospective relation to studies of human evolution has recently appeared, in fact, in a paper by C. S. Coon (1955).[2] It is safe to predict that attempts to assess the status vis-a-vis natural selection for many human variations heretofore considered normal will become a part of the work of students of anthropology. Here, once again, the study of abnormal or pathological states points the way to more general views of the meaning of human variety and its corollary, evolution.

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